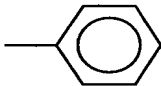
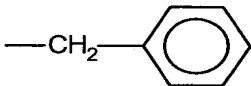


- I  
cont.
- A is CHOH or CHCl in arbitrary steric arrangement, CH<sub>2</sub>, C=O or 9(11) double bond,  
Y is hydrogen, fluorine or chlorine,  
Z is hydrogen, fluorine or methyl,  
R(1) is unsubstituted phenyl or phenyl substituted by one to three substituents selected from the group consisting of methoxy, chlorine, fluorine, methyl, trifluoromethyl, acetamino, acetaminomethyl, t-butoxy, t-butyl, 3,4-methylenedioxy, BOC-amino, amino and dimethylamino,  
(C<sub>1</sub>-C<sub>4</sub>)-alkyl is saturated,  
n is zero,  
m is 1,  
R(2) is linear or branched (C<sub>1</sub>-C<sub>8</sub>)-alkyl,  or   
R(3) is hydrogen or α- or β-methyl.
- 

### I. Status of the claims

Claims 11-22 are pending in this application. Claim 11 has been amended to correct an error in the chemical formula identified by the Examiner. Support for the amendment to the chemical formula appears in the correct formula shown on page 1 of the specification.

### II. Rejection of claims under 35 U.S.C. § 103(a) over Page

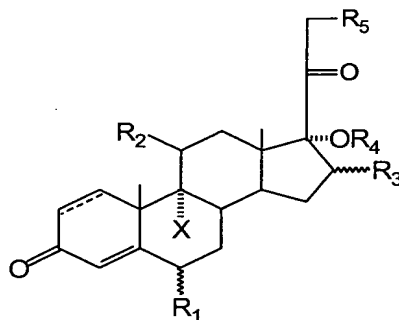
The Examiner rejected claims 11-17 as obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 4,655,971 to Page et al. ("Page"). The Examiner stated that Page teaches 17, 21-dicarboxylic esters of 4-pregnen-3,20-diones having either an oxo, halogen or hydroxy group in the 11-position and substituents in the 6, 9 and 16 positions that include those recited in the claims.

The Examiner indicated that the present claims differ from Page by reciting specific compounds wherein R(1) is substituted or unsubstituted phenyl. The Examiner nonetheless argued that Page discloses compounds of its formula (I) wherein R5 is

OC(O)-R', where R' is an alkyl group of 1 to 16 carbon atoms, a phenyl group or an aralkyl group of 7 to 8 carbon atoms such as  $-(CH_2)_{1-2}$ -phenyl. The Examiner concluded that applicant's claimed compound defining R(1) as a phenyl group was within the Page disclose and was obvious over Page. Applicants respectfully traverse this rejection.

**A. The Examiner has not established a prima facie case of obviousness**

Page discloses a process of preparing steroidal esters of the following formula:



where substituents R<sub>1</sub> to R<sub>5</sub> and X have the definitions set forth in Page. The R<sub>5</sub> substituent of Page corresponds generally to the portion of the side chain in the 21-position of the presently claimed compounds beginning with the oxygen that follows the CH<sub>2</sub> group. This portion of the claimed compound is -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl, with the phenyl being unsubstituted or substituted by the radicals recited in claim 11.

One skilled in the art would not have been motivated to make selections of substituents from Page to approximate the claimed invention. In order to have done so, and for the 21-position alone, one skilled in the art would have needed to define R<sub>5</sub> as R<sub>6</sub> (instead of as a hydroxyl group), define R<sub>6</sub> as OR<sub>7</sub> (instead of as a hydrogen or as one or two halogen atom substituents), where R<sub>7</sub> is an acyl group of the formula R'CO, and define R' as an aralkyl group of 7 to 8 carbon atoms (instead of a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group). Nothing in Page or the prior art as a whole guides the selections above. Absent any such guidance, Page does not render the present invention obvious.

The obviousness issue here is analogous to that decided in In re Baird, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994). In Baird, the applicant claimed a flash fusible toner comprising a binder resin which was a bisphenol A polyester containing an aliphatic

dicarboxylic acid selected from succinic acid, glutaric acid, and adipic acid. The Examiner rejected the claim as obvious over a patent to Knapp, which disclosed esterification of diphenol compounds and dicarboxylic acids. Recognizing that bisphenol A could have been derived when specific variables were chosen from the Knapp disclosure, the Examiner reasoned that the claimed compound "may be easily derived from the generic formula of the diphenol in Knapp and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the instant claim is to follow that formula." Id. at 1551. This rejection was upheld by the Board, but the Federal Circuit reversed.

The Baird court first noted that "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." Id. at 1552. Instead, the prior art must suggest the compound. Id. at 1552. In light of this test for obviousness, the court noted that "[w]hile the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables." Id. Apart from the generic disclosure in Knapp, the court also noted that the 15 specific diphenol compounds disclosed in Knapp were more complex than bisphenol A, rendering the Knapp disclosure as actually teaching away from the bisphenol A compound claimed by the applicants. Id. ("Indeed, Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols."). The court therefore ultimately concluded that the applicants had claimed a compound that was not taught or suggested by Knapp.

In light of the above, it appears that the Examiner's basis for the conclusion of obviousness, that "Applicant's claimed compound defining R(1) as a phenyl group is thus within the scope of the disclosure of Page et al.," seems to miss the points decided in Baird. The mere theoretical possibility of modifying the Page compounds, or of selecting particular substituents from the Page disclosure, by itself, is insufficient to establish a *prima facie* case of obviousness. In the Baird decision itself, the specific examples disclosed in the prior art could very well have been modified, using substituents that were disclosed as alternatives to each other in the prior art references,

to arrive at the claimed compound. Even so, nothing in the generic disclosure and specific examples motivated those substitutions, rendering those disclosures insufficient to create the *prima facie* case of obviousness. Furthermore, as explained above, Page's emphasis on the dissimilar aliphatic 21-position substituents in all the disclosed examples actually acts as a teaching away from the present invention, not a motivation to make the claimed invention.

Aside from Page's generic disclosure, the specific compounds taught in Page likewise do not provide the motivation to make the claimed compounds. In fact, each compound of Examples 1-28, the 10 specific compounds listed in Example 29, and the 5 compounds in Examples 30-34 all recite aliphatic group substituents in the 21-position, not -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl groups. Furthermore, and following the reasoning of In re Baird, Page's disclosure of these different specific compounds, which conspicuously lack the 21-position chain used by applicants, and do not contain any phenyl groups at all, actually teaches away from the present invention. See In re Baird, 29 U.S.P.Q.2d at 1552. See also MPEP § 2144.08 ("disclosure of dissimilar species can provide teaching away") (citing In re Baird).

With respect to the specific compounds of Examples 9 and 19 of Page cited earlier by the Examiner, applicants have already brought to the Examiner's attention evidence that would have counseled against using the compounds of Example 9 or 19 as starting points for making new compounds. That evidence, discussed in "Dermatika," Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, pp. 322-344 (1992), would have suggested to those skilled in the art that the compounds would have poor stability. Assuming that there is an expectation of similar properties between structurally similar compounds, those skilled in the art would have been dissuaded from using the compounds of Examples 9 and 19 as starting points for deriving new compounds, as they would have expected such new compounds to have poor stability as well. This evidence is relevant because it relates to the lack of motivation to make the claimed compounds.

**B. Claims 13 and 14 are each patentable over Page**

Claims 13 and 14 depend from claim 11 and further define the substituents A, Y, Z, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, R(1), R(2), and R(3) in the formula I. As with the compounds of the formula I, the Page disclosure would not have motivated one skilled in the art to derive either of these two more specific compounds.

With respect to claim 13, nothing in Page would have suggested the simultaneous selection of the following substituents:

X as hydrogen (instead of chlorine or fluorine);

R<sub>1</sub> as hydrogen (instead of fluorine, chlorine or  $\alpha$ - or  $\beta$ - methyl);

R<sub>2</sub> as hydroxyl (instead of halogen or oxo);

R<sub>3</sub> as hydrogen (instead of  $\alpha$ - or  $\beta$ - methyl);

R<sub>4</sub> as an acyl group of the formula RCO, in which R is an aralkyl group of 7 to 8 carbon atoms (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of a phenyl group);

R<sub>5</sub> as R<sub>6</sub> (instead of as a hydroxyl group),

R<sub>6</sub> as OR<sub>7</sub> (instead of as a hydrogen or as one or two halogen atom substituents),

R<sub>7</sub> as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and

aralkyl group as a C<sub>1</sub>-alkyl connected to unsubstituted phenyl.

With respect to claim 14, nothing in Page suggested the simultaneous selection of the following substituents:

X as fluorine (instead of hydrogen or chlorine);

R<sub>1</sub> as hydrogen (instead of fluorine, chlorine or  $\alpha$ - or  $\beta$ - methyl);

R<sub>2</sub> as hydroxyl (instead of halogen or oxo);

R<sub>3</sub> as  $\beta$ -methyl (instead of hydrogen or  $\alpha$ -methyl);

R<sub>4</sub> as an acyl group of the formula RCO, in which R is an aralkyl group of 7 to 8 carbon atoms (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of a phenyl group);

R<sub>5</sub> as R<sub>6</sub> (instead of as a hydroxyl group),

R<sub>6</sub> as OR<sub>7</sub> (instead of as a hydrogen or as one or two halogen atom substituents),

R<sub>7</sub> as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and

aralkyl group as a C<sub>1</sub>-alkyl connected to unsubstituted phenyl.

The rejection as it applies to claims 13 and 14 should therefore be withdrawn.

***C. The Unexpectedly superior properties of the claimed compounds would rebut any prima facie showing of obviousness***

Even if the Examiner had established a *prima facie* case of obviousness, the claimed compounds possess unexpectedly better properties over the prior art that would rebut any such *prima facie* showing. Compounds having a 21-aryl ester or 21-hetaryl ester, as claimed, "often exhibit qualities of effect which are clearly superior, as regards the local/systemic ratio of antiinflammatory effect, to those of structurally related corticoid 17,21-dicarboxylic esters or structurally related corticoid 17-alkyl carbonate 21-carboxylic esters which do not carry any aryl or hetaryl group in the 21-acid residue." Specification at page 5, lines 20-29. The class of compounds not having any aryl or hetaryl group in the 21-position obviously include compounds disclosed in Page. Moreover, the claimed compounds "surprisingly" exhibit "a very good ratio of local to systemic antiinflammatory effect, which ratio is often markedly superior . . . to that of known corticoid 17-alkyl carbonate 21-esters, which do not carry any aryl or hetaryl group in the 21-ester radical, such as, for example, 21-ester groups having a 21-alkyl group." Specification at page 13, lines 20-30. Detailed pharmacological testing

in support of these statements appears in the specification at page 15, line 12 to page 19, line 16.

These markedly superior and surprising properties of the claimed compounds constitute part of the invention "as a whole," that would rebut any *prima facie* case, if one had been established. In the most recent Office Action, the Examiner discounted the representations and testing in the specification as not persuasive because it "does not compare the closest prior art compound" to the claimed invention. In the Office Action, however, the Examiner cited, in addition to the compounds of Examples 9 and 19 of Page, new examples 3-5, 10, 13-15, 19-20 and 22-24. With the additional citation of those new examples, it is not clear to the applicants what particular example or examples the Examiner considers to be the closest prior art.

The one feature all the Page compounds have in common is an aliphatic group in the 21-position. The reference compound used in the comparative tests in the present specification, prednicarbate, likewise contains an aliphatic group in the 21-position. The comparative tests are thus relevant for purposes of comparing the claimed compounds versus compounds containing aliphatic group substituents in the 21-position.

### **III. Rejection of claims under 35 U.S.C. § 103(a) over Djerassi, Bowers and Oughton**

The Examiner rejected claims 11-17 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 3,021,429 to Djerassi et al. ("Djerassi"), or U.S. Patent No. 3,201,391 to Bowers ("Bowers") or U.S. Patent No. 3,133,940 to Oughton et al. ("Oughton"). In support of the rejections, the Examiner argued that the documents teach a number of different acyl groups attached to the 21-position of the compounds, including groups such as phenylpropionyl and phenylacetyl. The Examiner concluded that it would have been obvious to select such groups for the 21-position of those compounds to derive the claimed compounds. Applicants respectfully traverse this rejection.

Djerassi discloses compounds carrying an -OR' group in the position corresponding to the -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl group of the present claims. Djerassi defines R' as hydrogen or a hydrocarbon carboxylic acid acyl group of up to 12 carbon atoms derived from any carboxylic acid having up to 12 carbon atoms, saturated or unsaturated, or straight or branched chain, cyclic or mixed cyclic-aliphatic, substituted or not with methoxy, halogen or other groups. Djerassi at col. 1, lines 44-49. As examples, Djerassi lists acetates, propionates, butyrates, t-butyrate, hemisuccinates, enanthates, caproates, trimethylacetates, benzoates, phenoxyacetates, phenylpropionates, cyclopentylpropionates and  $\beta$ -chloro-propionates. Col. 1 at lines 49-53.

The general description in Djerassi at col. 1, lines 44-49, does not motivate one skilled in the art to use a -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl group as claimed. Furthermore, the phenylpropionate group, listed at col. 1, line 52, appears within a list of 13 various examples of carboxylic acid acyl groups. Djerassi contains no suggestion to choose the phenylpropionate group over any other groups listed in that passage. Furthermore, the example compounds of Djerassi all appear to use groups other than -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl in the 21-position, indicating, if anything, a lack of motivation to make the claimed invention.

Bowers discloses compounds carrying an -OR group in the position corresponding to the -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl group of the present claims. Bowers defines R as hydrogen or a hydrocarbon carboxylic acyl group containing from 1 to 12 carbon atoms. Bowers states that those acyl groups are derived from hydrocarbon carboxylic acids containing from 1 to 12 carbon atoms and may be saturated or unsaturated, straight chain or branched chain aliphatic, cyclic, cyclic-aliphatic, aromatic and may be substituted by hydroxy, an acyloxy group containing from 1 to 12 carbon atoms, an alkoxy group containing from 1 to 5 carbon atoms or by halogen such as fluorine, chlorine or bromine. Bowers at col. 1, lines 55-61. As examples, Bowers lists the acetate, propionate, butyrate, hemisuccinate, enanthate, caproate, benzoate, trimethylacetate, phenoxyacetate, phenylpropionate and  $\beta$ -chloropropionate. Col. 1 at lines 62-65.



The general description in Bowers at col. 1, lines 55-61, does not motivate one skilled in the art to use a -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl group as claimed. Furthermore, the phenylpropionate group, listed at col. 1, line 65, appears within a list of 11 various examples of carboxylic acid acyl groups. Bowers contains no suggestion to choose the phenylpropionate group over any other groups listed in that passage. Furthermore, the example compounds of Bowers all appear to use groups other than -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl in the 21-position, indicating, if anything, a lack of motivation to make the claimed invention.

Oughton discloses compounds carrying an -OR<sub>3</sub> group in the position corresponding to the -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl group of the present claims. Oughton defines R as "an acyl group." As examples, Oughton lists the acyl groups derived from carboxylic acids, such as acetyl, propionyl, benzoyl and phenylacetyl. Oughton at col. 2, lines 23-24. The general term "acyl group" does not motivate one skilled in the art to use a -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl group as claimed. Furthermore, the phenylacetyl group, listed at col. 2, line 24, appears only as one of several other listed groups. Oughton contains no suggestion to choose the phenylacetyl group over any other groups listed in that passage. Furthermore, the example compounds of Oughton all appear to use groups other than -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl in the 21-position, indicating, if anything, a lack of motivation to make the claimed invention.

The state of the art, subsequent to Djerassi, Bowers and Oughton, further highlights the lack of motivation to make the claimed compounds. For this purpose, applicants refer to the teachings of all patents cited by the Examiner in the Notice of Reference Cited that accompanied the Office action dated July 25, 1995 (Paper No. 7). None of the patents teaches the 21- position substitution used by applicants in the present claims. As the propriety of the Examiner's proposed modifications is determined by the teachings of the prior art as a whole, these patents are relevant to show that the state of the art did not motivate those modifications. These documents are particularly telling of a lack of motivation to make the claimed compounds, especially because none of them opted to use a 21-position phenylpropionate or

phenylacetate group, which the Examiner argued to be obvious in light of the earlier patents to Djerassi, Bowers and Oughton.

U.S. Patent No. 5,026,693 to Villax et al. teaches esters of 9 $\alpha$ -fluoro and chloro-corticosteroids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH<sub>2</sub> group. Y of Villax et al. can be, *inter alia*, OR<sub>1</sub>, where R<sub>1</sub> may be a benzoyl group (see col. 1, lines 64 and 65), but Y cannot be a group such as C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>-CO- or C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CH<sub>2</sub>-CO-. Therefore, Villax does not suggest compounds having -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl groups.

U.S. Patent No. 4,619,922 to Annen et al. teaches 6 $\alpha$ ,16 $\alpha$ -dimethyl corticoids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH<sub>2</sub> group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 37-39) but there is no suggestion of compounds having -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl groups.

Having effective filing dates subsequent to Page, these patents confirm that one skilled in the art, even when in possession of the Page disclosure, would not have been motivated to make the present compounds.

Likewise, a number of patents that may have effective filing dates prior to Page also would not have suggested the Examiner's proposed modifications. U.S. Patent No. 4,918,065 to Stindl et al. teaches corticoids having a substituent Z that corresponds to applicants' side chain in the 21- position following the CH<sub>2</sub> group. The Z substituent of Stindl et al. may be benzyloxy (see col. 1, lines 58-59) but there is no suggestion of -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl groups. U.S. Patent No. 4,701,451 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH<sub>2</sub> group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 40-41) but there is no suggestion of -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl groups.

U.S. Patent No. 4,645,763 to Annen et al. teaches 6 $\alpha$ -methyl corticoids having a substituent X that corresponds to applicants' side chain in the 21- position following the CH<sub>2</sub> group. The X substituent of Annen et al. may be acyloxy (see col. 1, lines 27-28) or benzyloxy (col. 8, lines 53-54), but there is no suggestion of -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-

alkyl]-phenyl groups. U.S. Patent No. 4,567,172 to Kamano et al. teaches 6 $\alpha$ -methylprednisolone derivatives having a substituent -O-R<sup>1</sup>, where R<sup>1</sup> may be -CO-R<sup>3</sup>, and R<sup>3</sup> may be a phenyl group (see col. 2, lines 40-63). This disclosure does not suggest compounds having -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl groups. Finally, U.S. Patent No. 4,555,507 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH<sub>2</sub> group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 38-39) but there is no suggestion of -O-CO-[(C<sub>1</sub>-C<sub>4</sub>)-alkyl]-phenyl groups.

In light of the above, the prior art as a whole would not have motivated one skilled in the art to make the claimed compounds. Absent a *prima facie* showing of obviousness, this rejection should be withdrawn.

Even if the Examiner had established a *prima facie* case of obviousness, the claimed compounds possess unexpectedly better properties over the prior art that would rebut any such *prima facie* showing. As mentioned earlier, compounds having a 21-aryl ester or 21-hetaryl ester, as claimed, "often exhibit qualities of effect which are clearly superior, as regards the local/systemic ratio of antiinflammatory effect, to those of structurally related corticoid 17,21-dicarboxylic esters or structurally related corticoid 17-alkyl carbonate 21-carboxylic esters which do not carry any aryl or hetaryl group in the 21-acid residue." Specification at page 5, lines 20-29. The class of compounds not having any aryl or hetaryl group in the 21-position obviously include compounds disclosed in Djerassi, Bowers and Oughton. Moreover, the claimed compounds "surprisingly" exhibit "a very good ratio of local to systemic antiinflammatory effect, which ratio is often markedly superior . . . to that of known corticoid 17-alkyl carbonate 21-esters, which do not carry any aryl or hetaryl group in the 21-ester radical, such as, for example, 21-ester groups having a 21-alkyl group." Specification at page 13, lines 20-30. Detailed pharmacological testing in support of these statements appears in the specification at page 15, line 12 to page 19, line 16.

These markedly superior and surprising properties of the claimed compounds constitute part of the invention "as a whole," that would rebut any *prima facie* case, if one had been established.

**IV. Return of 1449 form**

Applicants respectfully request that the Examiner return an initialed copy of the PTO 1449 form filed with the Supplemental Information Disclosure Statement of April 14, 1999.

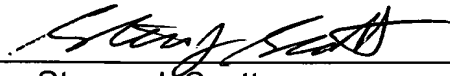
**Conclusion**

For the reasons given above, the Examiner has not established a *prima facie* case of obviousness. Even if such a *prima facie* case could have been established, the unexpectedly superior properties of the claimed compound over those of the prior art would rebut such a case. Applicants therefore respectfully request that the Examiner withdraw the rejection.

If there is any fee due in connection with the filing of this Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

By:   
Steven J. Scott  
Reg. No. 43,911

Date: December 16, 2001